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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/886,041	06/22/2001	Tai-He Xia	41491	5481

1609 7590 12/31/2002

ROYLANCE, ABRAMS, BERDO & GOODMAN, L.L.P.
1300 19TH STREET, N.W.
SUITE 600
WASHINGTON,, DC 20036

EXAMINER
BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
1646	11

DATE MAILED: 12/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/886,041	Applicant(s) Tai-He XIA et al.
	Examiner Michael Brannock	Art Unit 1646

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Oct 15, 2002 .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-25 is/are pending in the application.

4a) Of the above, claim(s) 9, 10, and 18-25 is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-8 and 11-17 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on Jun 22, 2001 is/are a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4/22/02
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Status of Application: Claims and Amendments

1. Claims 1-25 are pending.

2. Applicant is notified that the amendments put forth in Paper 6, 10/19/01, have been entered in full.

3. Claims 9, 10, 18-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 10, 10/21/02.

Drawings

4. The drawings are objected to as set forth in the attached PTO-948. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 3-8, 11-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as set forth below.

Claim 1 requires "a variant of GAVE3". The word "variant" renders the claim indefinite because is a relative term, and the specification does not set forth the degree of variation allowed, nor how the degree is to be measured; thus, the metes and bounds of the claim cannot be determined.

Claim 5 appears to claim a variant of SEQ ID NO: 1 and not SEQ ID NO: 1 itself, yet the claim does not literally claim a variant alone, i.e. the claim reads on any isolated nucleic acid of claim 1. Appropriate correction/clarification is required.

Claim 6 requires that an amino acid be substituted with a "functionally equivalent" amino acid. The phrase "functionally equivalent" renders the claim indefinite because the claim does not set forth what function the residue must be functionally equivalent to.

Claim 7 requires that the nucleic acid hybridize under stringent conditions. The term "stringent conditions" is confusing because it is a relative term and encompasses conditions of varying degrees of stringency - such conditions determining the bounds of the claim. However, the art does not provide an unambiguous definition of the term "stringent conditions" and neither is such a definition given for the term in the specification which puts forth the metes and bounds of the claim Applicant is seeking protection for. It is suggested that the claim recite the actual

conditions that applicant considers to be stringent, i.e., salt concentration and temperature conditions of incubations and washes.

Claim 8 requires that an amino acid sequence be 60% identical to SEQ ID NO: 1, yet SEQ ID NO: 1 is disclosed as a polynucleotide sequence. Additionally, the word "that" lacks antecedent basis in the claim, i.e. it is unclear what element in the claim is "that" element.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 3-8 and 11-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotides that encode a polypeptide of SEQ ID NO: 2 or fragments of a polypeptide of SEQ ID NO: 2, does not reasonably provide enablement for polynucleotides that do not encode a polypeptide or fragment of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims encompass polynucleotides that need only hybridize to SEQ ID NO: 1, yet may encode no active protein at all. While some of these polynucleotides could be used as specific probes to SEQ ID NO: 1, many would be expected to hybridize to other unrelated sequences. The specification has not taught how to use such polynucleotides nor how to make

polynucleotides that can be used as specific probes of SEQ ID NO: 1 but which are not 100% complementary to SEQ ID NO: 1. The specification provides general guidelines as to how to make other polynucleotides that specifically hybridize to SEQ ID NO: 1 (e.g. page 13) but does not provide any specific guidelines, nor examples, to enable the skilled artisan to determine which polynucleotides, of the practically limitless number encompassed by the claims, could be used to specifically hybridize to SEQ ID NO: 1; and nor has the specification provided guidance as to how to use the practically limitless number of encompassed polynucleotides that would not be expected to specifically hybridize to the polynucleotide of SEQ ID NO 1.

The state of the prior art as exemplified by Wallace et al. (in Berger and Kimmel, Eds., Methods in Enzymology, 152(432-442)1987) and by Sambrook et al., Molecular Cloning, p. 11.47, 1989, is such that determining the specificity of hybridization is empirical by nature and the effect of mismatches between two polynucleotides is unpredictable. There does not appear to be any working example of specific hybridization of variants given in the specification. In view of this, the empirical and unpredictable nature of the art, the lack of guidance with respect to appropriate modifications and the lack of guidance as to how to use other polynucleotides that fall within the scope of the claims, the specification does not teach one skilled in the art how to successfully make and use polynucleotides of the claimed scope without undue experimentation.

Claim 4 requires an allelic variant of SEQ ID NO: 1, yet the specification has not disclosed such variants. While the skilled artisan appreciates that allelic variants must exist in nature, the specification has provided no guidance as to where to find such variants, e.g. the

specification has not set forth any disorder or phenotype that may be associated with an allelic variant such the skilled artisan could obtain an allelic variant. Thus, the specification has merely invited the skilled artisan to begin a trial and error course of experimentation wherein individuals are randomly sampled to try to find allelic variants. Such random trial and error experimentation is unduly burdensome.

Furthermore, the claims encompass polynucleotides encoding polypeptide variants of the polypeptide of SEQ ID NO: 2, i.e. substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 2, yet the specification has not provided sufficient guidance as to how to make and use polynucleotides encoding polypeptides which are not 100% identical to the polypeptide of SEQ ID NO: 2, but which still retain a desired property of the polypeptide of SEQ ID NO: 2. Claim 7 requires polynucleotides comprising only portions of SEQ ID NO: 1. Thus, the vast majority of polynucleotides encode polypeptides that are amino acid sequence variants of SEQ ID NO: 2, i.e. amino acid substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 2, yet the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make. Furthermore, the specification has not provided guidance as to what properties of the allelic variants or sequence variants of the protein corresponding to SEQ ID NO: 2 might be desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Applicant has not defined a difference in structure or difference in function between the protein corresponding to SEQ ID NO: 2 and variants of said protein. If a variant of the protein corresponding to SEQ ID

NO: 2 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 2, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 2. Conversely, if a protein variant of SEQ ID NO: 2 need not have a disclosed property, the specification has failed to teach how to use such a variant.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Also, these or other regions may be critical determinants of antigenicity. It is well appreciated in the art of antibody production that it is

unpredictable which amino acids are critical antigenic determinants (see Alexander et al., Proc. Natl. Acad. Sci. 89(3352-3356)1992. Protein antigenicity can be significantly reduced by substitution of even a single residue. Further, even if an amino acid substitution does not destroy the activity of the immunizing protein, the substitution may significantly reduce the antigenicity of the protein (see the Abstract of Alexander et al.). The specification (e.g. page 20) does not provide sufficient guidance as to how to make antibodies that are specific to variants of SEQ ID NO: 2 that can be used for any specific purpose. The specification has not provided guidance as to natural variants that may exist, nor how to use antibodies specific to variants that might be created.

Although the specification outlines art-recognized procedures for producing variants (e.g. page 15), this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate the infinite number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide

activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

9. Claims 1, 3-8 and 11-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses a polynucleotide of SEQ ID NO: 1, yet the claims encompass polynucleotides not described in the specification, i.e. polynucleotides which comprise only portions of SEQ ID NO: 1, e.g. sequences from other species, mutated sequences, allelic variants, or sequences that have a recited degree of identity. None of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph. Although one of skill in the art would reasonably predict that these sequences exist, one would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of a single polynucleotide, that of SEQ ID NO: 1, encoding a polypeptide SEQ ID NO: 2, does not adequately support the scope of the claimed genus, which

encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural and functional features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polynucleotide sequence SEQ ID NO: 1, which is not sufficient to describe the essentially limitless genera encompassed by the claims.

The instant claims are not directed to that which is disclosed as essential to the invention, i.e. something that is homologous to the parent SEQ ID NO: 1 and has the function of the parent polynucleotide. Thus, with the exception of the of the polynucleotide of SEQ ID NO: 1, and other polynucleotides which encode a polypeptide of SEQ ID NO: 2, the skilled artisan cannot envision encompassed variants. Therefore, only a polynucleotides encoding a polypeptide of SEQ ID NO: 2, and polynucleotides *consisting* of fragments thereof, or polynucleotides consisting of fragments thereof and heterologous sequences (e.g. carrier or tag sequences), but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-8 and 11-17 are rejected under 35 U.S.C. 102(a) as being anticipated by WO/01/036473, published 25 May 2001.

WO/01/036473 disclose an isolated nucleic acid 100% identical to the instant SEQ ID NO: 1, see attached alignment, vectors, host cells, and methods of producing the encoded polypeptide, see the abstract. Note that the instant claim 5 does not specifically claim only variants of SEQ ID NO: 1.

12. Claims 1, 3, 5-7, 11-17 are rejected under 35 U.S.C. 102(b) as being anticipated by WO98/56820, published 12/17/1998.

WO98/56820 disclose an isolated nucleic acid encoding a variant of SEQ ID NO: 2, see attached sequence alignment. Wherein said variant contains at least one functionally equivalent amino acid residue substitution, e.g. the variant disclosed by WO98/56820 is a G-protein coupled receptor, as is the instant SEQ ID NO: 2, thus the mutations are functionally equivalent in that

both receptors retain G-protein binding activity. Vectors, host cells, and methods of producing the encoded polypeptide are also disclosed, e.g. page 7.

Conclusion

13. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Piacentini et al., Clin. Exp. Allergy, 28(561-567)1998 provide evidence that the determination of house dust mite antigen exposure (as taught on page 60, L14-26, of the instant specification) is a well established utility, see the entire Piacentini et al. document).

14. No claims are allowable.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m. The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

December 29, 2002

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600